A RETROSPECTIVE REVIEW OF CALCIUM CHANNEL BLOCKER POISONINGS FOR THE CALENDAR YEAR 1984

by

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A project submitted to the faculty of the
University of Utah in partial fulfillment of the requirements
for the degree of

Doctor of Pharmacy

College of Pharmacy

University of Utah

March 1987

UNIVERSITY OF UTAH COLLEGE OF PHARMACY

FINAL READING APPROVAL

TO THE DOCTOR OF PHARMACY COMMITTEE OF THE UNIVERSITY OF UTAH COLLEGE OF PHARMACY

I have read the clinical research project report of Mary Alice McCormick in its final form and have found that 1) its format, citations, and bibliographic style are consistent and acceptable; 2) its illustrative materials including figures, tables, and charts are in place; and 3) the final manuscript is satisfactory to the Supervisory Committee and is ready for submission to the Doctor of Pharmacy Committee.

4/22/87
Date

Chairman, Supervisory Committee

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UNIVERSITY OF UTAH COLLEGE OF PHARMACY

SUPERVISORY COMMITTEE APPROVAL

of a clinical research project report submitted by

Mary Alice McCormick

We, the undersigned, have read this clinical research project report and have found it to be of satisfactory quality for a Doctor of Pharmacy Degree.

4/22/87 Date	Chairman, Supervisory Committee
3/31/87 Date	Member, Supervisory Committee
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ACKNOWLEDGEMENTS

My deepest thanks to my family, Joanie, Judi, Carol & Nick, Jack & JoAnne, Paul, Dad, and especially Mom, for their courage and endless support in allowing me to stray so far from home. I didn't exactly get it done my way, but I couldn't have done it without you.

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INTRODUCTION

Verapamil was first introduced in the early 1960's as a smooth muscle relaxant with potent vasodilator properties.[1] Antiarrhythmic effects were demonstrated in the mid-1960's, but it was not until August, 1981 that the Food and Drug Administration (FDA) approved the intravenous form of the drug for clinical use. This action was followed by marketing of the oral form as an antianginal medication in March, 1982. Therapeutic benefits of verapamil have been attributed to its ability to block slow calcium channels, and in the years following its release, nifedipine and diltiazem, two agents with similar action, were given FDA approval.

Regulation of calcium is vital to a wide range of physiologic functions which include myocardial contractility, nerve impulse transmission, smooth muscle contraction and the secretory activity of exocrine glands. In the smooth muscle cell, calcium plays a dual role in excitation-contraction coupling. An excitatory impulse results in movement of extracellular calcium into the cell where it serves as a stimulus to initiate the release of intracellular stores of calcium from the sarcoplasmic reticulum. Once released, free cytoplasmic calcium binds to the regulatory molecule troponin and removes its inhibitory effect on actin and myosin, allowing them to interact and produce a contraction. The concentration of free intracellular calcium determines the degree of contraction of the entire muscle fiber.[2]

Intracellular stores of calcium are much greater in skeletal muscle than in cardiac and smooth muscle, therefore skeletal muscle is less affected by extracellular shifts of calcium into the cell. Conversely, cardiac and smooth muscle are dependent on transmembrane flux, requiring continual replenishing of calcium from extracellular sites. This dependency permits manipulation of the activity of these cells by calcium channel blockers.[1] Pharmacologically, the calcium channel blocker (CCB) drugs act to prevent excitation-contraction coupling, primarily by blocking the transmembrane movement of calcium ions.[1,2]

The CCB agents are a heterogeneous group of drugs that differ greatly in chemical structure and side effect profiles. Although much has been written about their varied side effects and therapeutic indications, limited information exists concerning their toxicity. Twenty-one human exposures describing overdoses with CCB agents have been reported in the English literature since 1977.[3-20] In 1984, Skoutakis and associates[3] reviewed six of the 17 literature reports then available and identified characteristic signs and symptoms in these poisoned patients. Specific therapeutic interventions were recommended by the authors, but the clinical utility of these recommendations was not confirmed. Clearly, more information about the toxicity of these agents was needed. Recently, an untapped resource of information about the toxicity of a wide range of agents, including CCB drugs, has become available, the American Association of Poison Control Centers (AAPCC) National Poisoning Data Base. This data base contained information on 730,224 human poison exposures during calendar year 1984. Four hundred eighty-one of these exposures involved CCB agents.[21] A review of the information on human exposures in the AAPCC database should provide additional epidemiological and toxicological data on CCB exposures not previously available.

The purpose of this research project was to retrospectively review the symptomatic CCB exposures reported to the AAPCC during calendar year 1984 and to describe the demographic characteristics, symptoms, treatment and outcome of acute overdoses with verapamil, nifedipine and diltiazem. This description should provide useful information for the health care provider about the management of patients with a CCB overdose.

Background Information

The AAPCC tested a national, voluntary, data reporting system for poison control centers in 1983. The system was subsequently made available nationally for use by poison control centers in 1984. The data collection system consists of:

1) a medical record and data collection form;
2) standard definitions for the data captured on the form;
3) a uniform data collection technique;
4) a uniform product identification code;
5) centralized data processing.

The AAPCC Cooperative Poison Center Report Form (Appendix A) is perforated vertically and separates into a medical record maintained by the individual poison center, and a scannable data collection portion. The separate parts are identified by the same unique serial number which allows the computer data to be linked to the medical record portion of the form. Participating poison centers submit their data to the AAPCC. Data may be sent to the AAPCC Data Compiling Organization on magnetic tape or computer disk or the data collection portion of the form may be sent to a central scanning service and then to the Data Compiling Organization. Data are compiled, analyzed and published yearly.

When a poisoning case is received by a poison center, pertinent data are gathered by the Poison Information Specialist (PIS) and recorded on the form. Included are a brief written history, assessment of severity, symptoms, follow up notes and outcome. In addition, certain of these data are captured for entry into a computer data bank by darkening scannable bubbles on the data collection portion of the form. The medical record portion of the form contains information not captured on the data collection portion of the form such as the time of the exposure, an estimate of the amount of product involved in the exposure, and the specific symptoms and duration of the symptoms experienced by the patient. Follow up generally occurs until symptoms have resolved, and when the case is brought to closure, the PIS selects a medical outcome representative of the symptoms experienced by the patient. The following medical outcome choices are available:

NO EFFECT: The patient developed no symptoms as a result of the exposure.

MINOR EFFECT: The patient exhibited some symptoms as a result of the exposure, but those symptoms were not life threatening. The symptoms resolved rapidly and the patient returned to a pre-exposure state of well being without residual disability or disfigurement.

MAJOR EFFECT: The patient exhibited some symptoms as a result of the exposure. The symptoms were life threatening or resulted in residual disability or disfigurement.

DEATH: The patient died as a result of the exposure or a direct complication of the exposure which was unlikely to have occurred had the toxic exposure not preceded the complication.

UNKNOWN, NONTOXIC EXPOSURE: The patient was lost to follow up; however, the exposure was likely to be nontoxic because the agent involved was nontoxic or the amount of the exposure (or route) was insignificant and unlikely to result in toxicity.

UNKNOWN, POTENTIALLY TOXIC EXPOSURE: The patient was lost to follow up and the exposure was significant and may have resulted in toxic manifestations.

The first four choices have known outcomes, indicating that poison center staff were able to follow the patient until symptoms abated or the outcome could be reasonably determined. The last two choices allow the PIS to predict the medical outcome when follow up is not possible. These medical outcomes are captured on the computer scannable section of the form and may be accessed through the national data base. Retrieval and review of the medical record portion of the data collection form of all CCB cases with a medical outcome other than "NO EFFECT" should provide information concerning patient characteristics, symptoms and treatment.

METHODS

The AAPCC allows access to data reported in the national data base only with the permission of the reporting poison center. Therefore, an initial letter was sent to poison centers in September 1985, requesting the cooperation of the center to allow access to data in the national data base. In October, centers not yet responding to this request were contacted by telephone, and verbal permission to include them in the study was obtained. Once permission was granted, the AAPCC forwarded a magnetic tape of all CCB exposures in the 1984 data base. This magnetic tape contained the data captured as scannable bubbles on the data collection portion of the form. A computer print-out was generated from these primary data and the information was utilized to identify symptomatic cases and exclude those with an outcome coded as "NO EFFECT".

In November 1985, each Center was sent another letter (Appendix B) with a list of that Center's CCB exposures. The letter asked that Center to send a copy of the medical record portion of the specified form to the investigator. Patient confidentiality was assured; however, the poison center was allowed to omit the name and phone number of the caller and patient before submitting the copy. Centers not responding to the letter were contacted by telephone in January 1986, and asked to send copies of the specified forms by March 1, 1986.

The medical record portion of the data collection form served as a second source of data concerning CCB exposures during 1984. Information was primarily abstracted from this source because of the additional descriptive information available in this section. Each form was reviewed and data were abstracted and entered into a personal computer, in a standard format. Each case was searched for fifteen items:

1) case identification number
2) reporting center code number
3) outcome
4) age
5) sex
6) time of call
7) date of call
8) time lapse since exposure
9) product
10) dose ingested
11) treatment site
12) presence of symptoms at time of poison center contact
13) drug history
14) signs and symptoms
15) treatment

Unique designations were originally assigned to "positive findings", "negative findings", and "missing data". Using hypotension as an example, a "positive finding" was defined as a systolic blood pressure less than 90 mm Hg or notations of "hypotensive" on the medical record portion of the data collection form, while a "negative finding" would be represented by a blood pressure reading of 120/80 mm Hg or notes of "normotensive" on the record. The "missing data" category was used to designate a chart lacking information concerning the patient's blood pressure. The latter two categories were excluded after initial analyses because "negative findings" were infrequently charted on the forms and "missing data" provided no useful information. Criteria were also developed to extract the dose ingested when a range of doses was noted on the form, for example, "20-30 verapamil 80 mg." When this occurred, the lowest dosage was used in order to avoid overestimation of the minimal toxic dose. When abstracting gastrointestinal signs and symptoms, a notation of vomiting was considered related to the CCB only if it occurred prior to use of gastrointestinal decontamination measures.

The Statistical Package for the Social Sciences (SPSS) was utilized to analyze the data. Cross tabulations were generated and chi-square analysis was performed during preliminary analyses. After implementation of an extensive case exclusion process, the 50 remaining cases did not meet the criteria for use of these analytical tests. Simple descriptive analyses including mean, range and frequency, were used because the data could best be described by these tests.

RESULTS

Cardiovascular drugs comprised 6,740 of the human poison exposures reported to the AAPCC National Data Base during 1984. Four hundred eighty-one of these exposures involved CCB agents [21] and 50 (10.4%) of the CCB cases are reported here. Figure I illustrates the reasons for exclusion of the cases. Two hundred forty-two of the cases had a medical outcome categorized as "NO EFFECT"; these cases were excluded because the patients did not develop symptoms. Thirty-nine case reports were unavailable from six centers which refused to participate in the study. Twenty-one cases were irretrievable by poison centers which agreed to participate. Seven cases, originally reported as CCB exposures, were excluded because the patient had not ingested a CCB; five cases were not submitted on the AAPCC form as requested; one case was an informational request rather than an exposure; one case was a duplicate entered into the data base twice; and one case involved an animal exposure rather than a human exposure.

Thus, 164 cases were reviewed and initially analyzed. This analysis revealed the confusing nature of information about symptoms, treatment and outcome on the forms where CCB drugs were taken concurrently with another drug. Frequently, it was not possible to determine if the symptoms reported were attributable to the CCB, the other agent taken concurrently or to some interactive effect. Therefore, 43 cases were excluded. It also became apparent that exposures with "UNKNOWN" outcomes lacked follow up and specific information. Subsequently, 71 cases with "UNKNOWN" outcomes were also excluded leaving 50 cases which were analyzed and reported. Twenty poison centers representing 17 states contributed these

50 cases.

Table I lists the age, sex and reason for exposure by product. The patients studied ranged in age from one to 73 years with a mean of 25.5 years. Seventeen (34%) of the exposures involved children less than five years of age; eight children were one year of age, seven were two years old, and the remaining two were four years old. Thirty-one subjects were adults with a mean age of 41 years, however, the age was not recorded in seven cases. Two patients, each 15 years old, were included in the adult category for analytical purposes. Eighteen (36.7%) subjects were male, 31 (63.3%) were female, and the sex was unrecorded in one pediatric case. Females predominated in the adult category by a ratio of two to one, while the children were equally divided by sex.

Diltiazem was ingested in seven cases (14%), nifedipine was ingested in 13 cases (26%) and verapamil accounted for the remaining 30 cases (60%). All children accidentally ingested the medication, 18 adults intentionally overdosed, 10 adults accidentally overdosed and five patients experienced an adverse drug reaction to a prescribed therapeutic dose. Seven of the 17 children were found to have ingested a grandparent's medication and 21 of the 33 adults ingested medication prescribed for them. This includes six of the 18 patients intentionally overdosing with a CCB. Eight subjects were prescribed the medication for control of angina or cardiac arrhythmias, three received the medication for migraine headache, while the diagnosis was unknown for the remaining ten cases. It is likely that many of these patients had been taking their medication chronically before the overdose occurred since the medication was noted to be newly prescribed in only four cases.

The time which had elapsed between the patient's exposure and initial contact with the poison center was recorded for 38 of the acute ingestions and is described in Table II. Twenty-one percent of the incidents happened "now" or "just prior to the call". Thirty-four percent of the callers contacted the poison center within five minutes of the exposure and 58% sought help by 30 minutes. Within one hour of the exposure, 71% of the calls had been received, 82% called within two hours, 87% within three hours, 92% by four hours, and 97% had been received within six hours of the exposure. Excluded from the table were four adult exposures which occurred over an extended period of time, five cases for which the time since ingestion was unknown, and three cases for which the time was unrecorded.

When a child was involved in an exposure, contact with the poison center was established more quickly than with adults. An average of 15 minutes elapsed between exposure and a call to the poison center for pediatric cases while the average time increased to 117 minutes for the adult group. When intentional overdoses were analyzed separately, the average time to contact the poison center increased to 182 minutes while adults with accidental ingestions called an average of 27 minutes after the exposure.

Table III lists the average dose of drug ingested by the patient for the pediatric and adult groups. Only 37 of the 50 patients had this information recorded. In children, the average dose was 38 mg. for diltiazem, 10 mg. for nifedipine and 710 mg. for verapamil. The average amount of drug ingested by adults was 60 mg. for diltiazem, 87 mg. for nifedipine, and 2,871 mg. for verapamil. When suicidal patients were considered separately, the average dose increased to 225 mg. for nifedipine and 3,677 mg. for verapamil.

One patient ingesting nifedipine exceeded the maximum daily therapeutic dose, but verapamil was the only product ingested in an average amount which exceeded this maximum recommended dose. Children ingested 1.5 times the maximum daily adult dose on average, but one child who ingested less than four times the maximum therapeutic daily dose died. Verapamil is approved for pediatric use as an intravenous drug, but oral pediatric dosing guidelines are not available for any of the CCB drugs. On average, the adults ingested six times the maximum daily therapeutic dose. When analyzed separately, those patients intentionally overdosing influenced this average by ingesting eight times the maximum daily therapeutic dose.

The minimal toxic dose of diltiazem in children was 60 mg. which produced a petecchial rash and arrhythmias in a two year old child. The ingestion of 10 mg. of nifedipine produced symptoms in three children; one became drowsy, another exhibited facial flushing and a third developed hypotension. Verapamil produced spontaneous vomiting in one child and "tiredness" in another following the ingestion of less than one tablet; the ingestion of 240 mg. by a two year old child produced cardiac arrhythmias. A dose of 1,600 mg. in a 15 month old male resulted in death. Some adults experienced an adverse drug reaction from a therapeutically prescribed dose of their own medication; 60 mg. of diltiazem produced transient dizziness and shakiness in one patient and a headache in another; a dose of 80 mg. of nifedipine produced transient mild hypotension in an adult and a dose of 80 mg. of verapamil in an adult produced transient central nervous system depression, heart rate changes and mild hypotension. More serious effects occurred at the upper end of the therapeutic dosing range; intentional overdoses of 150 mg. of nifedipine and 480 mg. of verapamil in adults produced more severe hypotension requiring intravenous fluids to correct the condition. Vasopressors were also required

to treat severe hypotension produced after an ingestion of 800 mg. of verapamil, and a dose of 1,920 mg. resulted in death in a 37 year old female.

Thirty (60%) of the patients had developed symptoms by the time a call was placed to the poison center. Thirteen were asymptomatic at initial assessment, while this information was missing for the remaining seven cases. All patients eventually developed symptoms. Table IV lists the toxic effects which occurred in these 50 symptomatic patients. Forty-four percent of the subjects studied developed cardiovascular effects. Eleven (21.6%) of the subjects demonstrated changes in heart rate. Five developed bradycardia, while six patients were tachycardic. All of these patients had taken verapamil. Nineteen patients (38%) exhibited hypotension after ingesting a CCB; two of these were children. This includes half (15 of 30) of the verapamil patients and one-third (4 of 13) of the patients exposed to nifedipine. None of the subjects ingesting diltiazem became hypotensive. Thirteen patients (26%) developed abnormal electrocardiograms during the course of the exposure. A two year old child had blocked paroxysmal atrial tachycardia, an irregular S-T segment, a prolonged P-R interval and experienced bigeminy for 20 minutes after ingesting 60 mg. of diltiazem. The remaining 12 patients developed arrhythmias after ingesting verapamil. These included four patients with junctional rhythm; one child with A-V dissociation, prolonged P-R interval and variable block; another patient exhibited Mobitz II type arrhythmias concurrent with A-V dissociation; one patient had paroxysmal atrial contractions; and another demonstrated first degree heart block. The remaining abnormalities, demonstrated in four patients, were a widened QRS interval, ventricular fibrillation, ventricular tachycardia and "multiple cardiac arrhythmias" noted in the child who died.

Central nervous system effects occurred in twenty-four subjects (48%). These symptoms were described as lightheadedness, dizziness, headache, shakiness, sleepiness or drowsiness, lethargy, ataxia, agitation and combativeness. Those persons ingesting nifedipine were most likely to experience these effects; ten of the 13 subjects exposed to nifedipine had central nervous system symptoms. Verapamil produced central nervous system effects in 11 patients while these effects occurred in three patients taking diltiazem. Only 18% of the children manifested central nervous system effects while 64% of the adults had these effects.

Four patients developed dermal reactions after ingestion of a CCB. A two year old child exhibited "red lips" and developed petecchiae across his chest after ingesting 60 mg. of diltiazem and a 66 year old woman developed pruritis and a macular rash over her trunk and extremities after two weeks of chronic therapy with diltiazem. Two patients ingesting nifedipine also manifested dermal effects. An 18 month old female developed red, hot cheeks, red eyes and cold hands after sucking on a 10 mg. capsule of nifedipine, and a 55 year old male was "flushed all over" after taking two Procardia® which he mistook for Doan's Pills®.

Eleven (22%) subjects, two ingesting nifedipine and nine exposed to verapamil, developed gastrointestinal symptoms; four of these were children. Nausea and spontaneous vomiting were the symptoms noted, although one child who died after ingesting 1,600 mg. of verapamil had diffuse gastrointestinal hemorrhage on autopsy.

A total of six effects listed as other occurred in four patients. Metabolic abnormalities were documented on the records of two patients (4%). An adult ingesting 6,000 mg. of verapamil had a serum glucose concentration of 349 mg./dl. and a child ingesting 1,600 mg. of verapamil had a serum potassium of 10 mEq/l. This same child developed acute renal failure and adult respiratory distress syndrome prior to his death. The second adult demonstrated cyanosis of uncertain etiology requiring intubation and a third developed digital ischemia.

Table V illustrates the reason for exposure, treatment site, and disposition of the 50 patients. Thirty-six (72%) patients were evaluated and treated in an emergency department; 25 adults and eleven children are in this group. Twenty-one patients, 16 adults and five children, were subsequently admitted as inpatients for continued care, while 12 patients were treated and released from the emergency department, and three patients died. All 18 of the adults intentionally overdosing with a CCB were evaluated at a health care facility; 15 were admitted for medical care, one was admitted for psychiatric evaluation, and two patients died. These latter two patients did not survive treatment beyond the emergency room. The pediatric death occurred in the intensive care unit.

Table VI shows the number of patients receiving gastrointestinal decontamination and the specific therapy used. Forty-four percent of patients received some type of gastrointestinal decontamination. Although these treatments were frequently recommended by the PIS, it could not be determined if gastrointestinal decontamination was utilized for the remaining 28 patients. Sixteen patients (32%) received ipecac syrup; five adults and eleven children are included in this group. Four adults and one child received gastric lavage; the child also received ipecac syrup. Nine adults and two children were given activated charcoal, while four adults and three children received a cathartic. Only four patients, two adults and two children, received full gastrointestinal decontamination which includes ipecac or lavage, followed by activated charcoal and a cathartic.

Although all patients developed symptoms, not all patients required treatment. Table VII lists specific treatments used in 21 of the 50 patients. Seven patients, who had all ingested verapamil, were given calcium salts for treatment of hypotension or arrhythmias. Four of these patients, including one 18 month old child who developed arrhythmias after ingesting verapamil, received calcium gluconate; however, the dose was undeterminable. Two patients received unspecified "calcium", with dosage not recorded. One patient received calcium chloride, which reverted a widened QRS interval, although this patient later died.

Seven adults (14%) received a fluid challenge to increase blood pressure; two of these patients had taken nifedipine and five had ingested verapamil. Five patients received normal saline, however, the type of fluid replacement was unspecified in the other two cases. Two patients ingesting nifedipine and one ingesting verapamil, had a positive response to this fluid challenge and required no further treatment for hypotension. Nine patients received vasopressors for hypotension, four after receiving a fluid challenge; all patients had ingested verapamil. Seven patients received dopamine alone; one patient received isoproterenol plus dopamine and one patient received isoproterenol and norepinephrine. These latter two patients died; these same two patients had pacemakers inserted. One patient was "defibrillated for atrial fibrillation"; three patients received cardiopulmonary resuscitation but ultimately died.

Six patients received five medical treatments other than those previously noted. One patient, who developed a rash after taking diltiazem chronically, was prescribed diphenhydramine and triamcinolone acetonide for the reaction. Five patients ingesting verapamil received other remedies; two were prescribed oral fluids, one patient received 10 units of insulin for an elevated blood glucose, another received lidocaine for ventricular tachycardia; and an unspecified extracorporeal method to enhance verapamil elimination was attempted in the child who died.

DISCUSSION

During 1984, the AAPCC gathered data on 481 exposures to CCB agents. Fifty of these cases in which the outcome was known and follow up occurred have been reviewed. This report best describes the effects of verapamil since this drug was ingested consistently in much larger amounts than nifedipine and diltiazem. Verapamil was ingested predominantly by adults with suicidal intent. The two hour average time delay between exposure and poison center contact for the adult cases indicates the purposeful intent of many of these adult patients, since suicide attempters tend to delay in seeking medical attention.[22, 23] The delay in contacting the poison center would also contribute to a greater likelihood of serious symptoms developing since greater absorption of the medication could occur. The large number of suicidal patients admitted for medical care also reflects the serious nature of the large doses ingested.

Minimal toxic doses of CCB agents, based on cases described in this report, are within the therapeutic dosage range. The five patients who experienced an adverse drug reaction after ingesting a therapeutic dose, and the ten adults who mistakenly took a double-dose of their own medication and developed symptoms demonstrate the low therapeutic index of the CCB drugs. More serious effects occurred for both nifedipine and verapamil at the upper limit of the recommended daily therapeutic dosing range. The manufacturer of nifedipine recommends a daily dose of 120-180 mg. A 50 year old female with a history of unspecified cardiac disease ingested 150 mg. of nifedipine and required treatment for the hypotension that occurred. The maximum recommended daily dose of verapamil is 480 mg; an adult ingesting this dose developed gastrointestinal symptoms and hypotension requiring treatment with intravenous fluids.

A difference appeared among the three CCB agents in the frequency of occurrence of central nervous system effects. Patients ingesting nifedipine exhibited a 77% frequency of these symptoms as opposed to 43% for diltiazem and 37% for verapamil. At therapeutic doses, nifedipine also demonstrates the highest incidence of central nervous system effects with a rate of 8-26% reported for dizziness and headache.[24]

When reviewing supportive treatments used for the 50 study patients, an appropriate explanation for the small percentage of patients receiving some type of gastrointestinal decontamination is likely twofold. First, 15 patients presented with symptoms after ingesting a double dose or taking a therapeutic dose of a newly prescribed medication. Since the number of tablets or capsules ingested was small, the expected yield from gastrointestinal decontamination would be minimal. None of these study patients received any form of gastrointestinal decontamination. Second, a larger number of patients actually may have received gastrointestinal decontamination than was documented. For those patients treated in a health care facility, ipecac syrup or lavage, activated charcoal and a cathartic, were recorded consistently as recommended, but documentation concerning the actual administration of these therapies was often lacking.

The most frequently utilized form of decontamination was induction of emesis with ipecac syrup. In a few instances, lavage was recommended in preference to induction of emesis with ipecac syrup because of the possibility of rapid onset of central nervous system depression or cardiovascular complications. This is especially important for the pediatric patient who chews nifedipine soft gelatin capsules, the contents of which are absorbed sublingually and have an onset of effect estimated in minutes.[24] One 18 month old female who sucked on a nifedipine capsule developed red cheeks within 20 minutes and appeared dizzy 40 minutes after the ingestion. This rapid onset of effect may prove lethal to patients taking large overdoses. If serious symptoms develop within one-half to two hours after exposure, the optimal benefits of gastrointestinal decontamination may be hindered when treatment is delayed. Early administration of gastrointestinal decontamination is especially important for overdoses involving drugs with a rapid onset of effect such as the CCB agents.

The role of calcium salts as antidotes for CCB overdoses is currently unknown. Calcium salts are frequently recommended to treat hypotension and cardiac dysrrhythmias associated with CCB overdoses, but actual evidence to support their efficacy is conflicting. Several authors [3,6,9,11,12,16-19] attributed the clinical improvement of their patients to the administration of calcium salts, although closer scrutiny revealed that intravenous fluids, vasopressors, or other therapeutic interventions were used simultaneously. Thus, the improvement could not always be definitively attributed to the administration of calcium salts. Others administered calcium salts without comment as to their effect [8,15] and a third group noted a distinct lack of therapeutic benefit when calcium salts were given.[10,13] Several mechanisms exist by which CCB drugs may prevent excitation-contraction coupling, yet it is not known if any of these mechanisms can be competitively reversed by the addition of calcium salts. Further research is needed to determine the role of calcium salts as antidotes in CCB overdoses.

When reviewing the cases in which patients required treatment for hypotension, it is likely that the use of a fluid challenge as a specific treatment is under reported. Standard treatment for acutely hypotensive patients in a hospital is to place the patient in the Trendelenberg position, followed by an intravenous fluid challenge and administration of vasopressors, if necessary. Only four patients were noted to have received a fluid challenge prior to the administration of vasopressors, yet nine patients received vasopressors. Since two patients ingesting nifedipine and one taking verapamil responded to a fluid challenge, the number of patients receiving a fluid challenge should exceed those receiving vasopressors. Only one patient was noted to have been placed in the Trendelenberg position. Eleven of nineteen patients developing hypotension received a fluid challenge or vasopressors or both, suggesting that hypotension was clinically significant in greater than half of the patients.

Three of the four deaths identified in the national data base are included in the study cases and are described in detail in Appendix C. All deaths occurred after the ingestion of verapamil. The delay in seeking medical attention and receiving gastrointestinal decontamination may be important in these cases. For example, a 15 year old male ingesting 3,600 mg. of verapamil survived after arriving at a health care facility within 30 minutes of exposure. He immediately received gastrointestinal decontamination. Another adult survived a dose of 6,000 mg. of verapamil with prompt gastrointestinal decontamination and supportive care in the emergency department, although the time since ingestion was unknown. Paramedics were at the scene 30 minutes after a patient ingested 21,600 mg. of verapamil, but rapid deterioration prevented gastrointestinal decontamination in this patient and he died. The other adult who died arrived at a health care facility at an unknown time after ingestion of 1,920 mg. of verapamil. Inability to stabilize this patient also precluded the administration of gastrointestinal decontamination measures. The pediatric death occurred after ingestion of 1,600 mg. of verapamil. The time of ingestion and use of gastrointestinal decontamination were unknown in this case. One of the 50 cases appears to contradict the argument that prompt gastrointestinal decontamination is important to survival of the patient. A 19 year old female who ingested 5,600 mg. of verapamil and was not evaluated at a health care facility until eleven hours after exposure did not develop severe toxicity; she was described as "shaky and dizzy and vomiting all night". By her history, she was treated and released after an unspecified cardiac evaluation was performed in the emergency room. Although gastrointestinal decontamination measures were not utilized in this case, reasons which can be suggested to account for the mild course exhibited by this patient include inaccurate estimate of the amount ingested, or prolonged vomiting and subsequent removal of the drug secondary to this effect. In spite of this case, early utilization of gastrointestinal decontamination techniques and prompt referral to a health care facility are prudent measures to be considered after ingestion of a large amount of verapamil.

Some medications prescribed for adults, such as Lomotil® and Catapres® may be more toxic in children than adults.[25, 26] Since the half-life of verapamil may be longer in children than adults after an oral dose,[27] an attempt was made to determine if pediatric subjects differed from the adults. For the majority of the organ systems involved, children developed toxic effects at a lower rate than the adults. None of the children developed heart rate changes, and a smaller percentage experienced hypotension and arrhythmias than the adults. The lower percentage of central nervous system effects which occurred in the pediatric group may be explained by the subjective nature of these effects. Central nervous system symptoms included headache, dizziness and lightheadedness, which are difficult to assess in young children, although two parents reported effects described as "dizziness, bumping into things", and "tiredness", and an emergency department nurse described a child as "sleeping". Effects may also have occurred less frequently because of the quicker response time in the pediatric group. For accidental ingestions, the response time in children was half that of the adult response time. Gastrointestinal decontamination measures instituted earlier may have prevented absorption of the drug ingested.

For those organ system effects rarely reported, the pediatric sample is biased by the case involving the fifteen month old child who died after ingesting verapamil. Three of his post-mortem findings were unique: adult respiratory distress syndrome, acute renal failure and diffuse gastrointestinal hemorrhage. This child also displayed hyperkalemia. No surviving patients were known to exhibit any of these findings and autopsy reports were not available for the two adult deaths for comparison. These effects cannot be directly attributed to the CCB although prolonged hypotension due the large dose of verapamil may have been contributory.

Children experienced less severe symptoms than adults as evidenced by the minimal treatment required. None of the children received a fluid challenge, vasopressors, or a mechanical pacing device, confirming the mild and transient nature of the hypotension and arrhythmias reported. The large number of children treated in a health care facility may be explained by the lack of FDA approval for pediatric oral use of the CCB drugs. Lack of therapeutic dosing guidelines and experience with these medications in the pediatric population may have resulted in referral to a health care facility rather than observation in the home.

Based on the cases reviewed in this report, the minimal toxic dose of CCB drugs for pediatric patients appears to be a therapeutic adult dose. The average amount of CCB ingested by the pediatric patients was much less than that ingested by the adults, but a child died after ingesting less than four times the maximal therapeutic daily dose of verapamil. More accurate estimation of ingested doses should be based on a milligram per kilogram amount or serum drug concentrations. These calculations were not possible since weights of victims were not routinely recorded and serum drug concentration assays are not readily available.

Comparison of Cases to Literature Reports

The twenty-one literature case reports [3-20] involving CCB ingestions have not been reviewed collectively. As seen in the study cases, the literature cases contained a large number of verapamil exposures. In order to better describe overdoses by patients with suicidal intent ingesting verapamil, the literature cases were reviewed in a format similar to that utilized for analysis of the study cases. Eleven literature reports were excluded; seven cases involved polydrug exposures, one case each involved diltiazem and nifedipine rather than verapamil, one case involved an accidental pediatric exposure and the last case was a pathology report. Ten of the literature reports and fifteen study cases involving verapamil were compared.

The average age of patients reported in the literature was 27 years (range 14-68) compared to a mean age of 32 years (range 15-59) for the fifteen verapamil cases reported in 1984. There were 11 females and four males in the study cases compared to seven females and three males in the literature series. These data correlate with the intentional nature of the ingestions; most suicide attempters are under 30 years of age and the predominance of female over male patients who attempt suicide occurs in almost all countries and time periods studied. [22] The average dose ingested in the literature reports was comparable to that found in the AAPCC data base, 3,333 mg. in the literature and 3,683 mg. in the study cases.

Cardiovascular effects occurred most frequently in both the study cases and literature series with 92% of the patients developing symptoms in this category. Hypotension was the most frequent sign noted in 100% of the literature cases, with arrhythmias occurring next at a rate of 90%; hypotension and arrhythmias occurred at equal rates of 73% in the study cases.

Heart rate changes occurred at a rate equal to arrhythmias for the literature patients but occurred in only 47% of the study patients.

Effects occurred in a variety of other organ systems including the central nervous system where symptoms occurred in 48% of the combined cases. One patient in the literature series developed generalized tonic-clonic seizures after ingesting 2,000 mg. of verapamil. This effect was not reported in the study cases. Gastrointestinal symptoms were reported in only 10% of the literature cases while one-third of the study cases reported these effects. Hyperglycemia and cyanosis were described in both groups, although occurring infrequently. Metabolic acidosis was also described in the literature series.

All patients in both series were evaluated and treated at a health care facility. Half of the literaure patients received some type of gastrointestinal decontamination while this treatment was recorded in 70% of the study cases. Only one patient in each series received full gastrointestinal decontamination. The benefit of early gastrointestinal decontamination and transport to a health care facility with large ingestions of verapamil is supported in both series. The study cases include the two patients described earlier who ingested 3,600 mg. and 6,000 mg. of verapamil and survived with prompt initiation of gastrointestinal decontamination procedures and supportive treatment at a health care facility. Another patient in the literature series survived after ingesting 5,600 mg. of verapamil. She received full gastrointestinal decontamination after transport to a health care facility, although the time between ingestion and decontamination was unknown.

Eighty percent of the literature patients and one-third of the study patients received intravenous calcium salts. As with the AAPCC cases, several treatments were given concurrently with the calcium salts in the literature cases. Clinical improvement could not always be attributed solely to the administration of calcium although many of the authors felt this to be true.[3,6,9,11] In contrast to these claims, Immonen and coworkers[10] specifically described the lack of a therapeutic benefit from the administration of calcium gluconate in a 68 year old female who ingested 6,400 mg. of verapamil; they concluded that the usefulness of calcium gluconate in the treatment of verapamil poisoning needs further study with higher doses of calcium. This patient received a ten hour infusion of calcium gluconate in which 10 ml. of a 10% solution were infused every two hours.

Toxic effects requiring specific treatments developed most frequently within the cardiovascular system in both series. A fluid challenge was given to 20% of the literature patients and one-third of the study patients. Forty percent of the literature cases and 60% of the study cases reported the use of vasopressors. Dopamine predominated as the vasopressor of choice in both series, although some patients required the addition of a second vasopressor; isoproterenol was used in five cases while norepinephrine, epinephrine and metaraminol were used in one case each. Four patients in the literature series received atropine for bradycardia; only one patient responded. Atropine appeared ineffective in increasing the heart rate sufficiently to avoid the use of cardiac pacing devices since three of the four patients receiving it required pacemakers. Although the two study patients requiring pacemakers died, the literature series reports better success with three of four patients surviving.

One adult death occurred in the literature series.[14] This case involved a seventeen year old female who was admitted one to two hours after ingesting of an unknown amount of verapamil. She was cyanotic, had fixed, dilated pupils, no detectable blood pressure and was found to have complete heart block with a rate of 30 beats per minute and narrow complex escape described on her electrocardiogram. She received a continuous infusion of calcium gluconate; dopamine, isoproterenol and epinephrine were administered to raise her blood pressure. Atropine was given to increase her heart rate prior to insertion of a cardiac pacemaker. Cardiopulmonary resuscitation was required. The patient died 19 hours after admission. The choice of vasopressors in this case parallels their use in the other cases in which they were required. Dopamine is favored as the initial vasopressor with isoproterenol most frequently added when a second vasopressor became necessary. The renal sparing effect of dopamine makes it a rational first choice as a vasopressor and the inherent beta agonist effects of isoproterenol more directly counteract the hypotension and bradycardia produced by verapamil.[2]

Treatment Recommendations

After describing the 50 AAPCC study cases and comparing the intentional verapamil overdoses to those in the literature, a summary of organ system effects follows and treatment recommendations are provided for patients acutely overdosing with verapamil. Regardless of the dose ingested, psychiatric intervention should be provided to the patient if the overdose intent was purposeful.

Minor toxicity occurs at doses of < 480 mg. of verapamil for adults and < 80 mg. for pediatric patients. Gastrointestinal effects may occur; nausea and spontaneous vomiting are commonly reported. Approximately half of the patients develop mild central nervous system effects such as lightheadedness, dizziness, headache, sleepiness or drowsiness, lethargy and ataxia. Transient heart rate changes also occur at these doses; bradycardia is more common than tachycardia. Patients ingesting these amounts of verapamil may be observed at home. Gastrointestinal decontamination is not necessary. If these minor symptoms develop, they will occur within one to two hours and should abate within six to eight hours of exposure. The effects are transient and medical intervention should not be required.

Moderate toxicity to verapamil occurs in the adult at doses of verapamil between 480 mg. and 800 mg; children develop similar effects at doses between 80mg. and 240 mg. Gastrointestinal and central nervous system effects are comparable to those described at lower doses, but more serious cardiovascular effects occur within these dosage ranges. Hypotension will likely be present, however, this effect may be transient and not all patients require treatment. Hypotension requiring a fluid challenge occurred in one adult ingesting 480 mg. and an 800 mg. dose required administration of dopamine. The patient should be transported to a health care facility; if transport by private vehicle will delay treatment longer than twenty minutes, ambulance transport should be utilized because symptoms may develop rapidly. Full gastrointestinal decontamination should be performed promptly. Consider lavage over induction of emesis with ipecac syrup; rapid decontamination is necessary since cardiovascular compromise may develop abruptly. Blood pressure readings should be taken every 15 minutes for the first two to four hours. If hypotension develops, intravenous fluids and vasopressors may be necessary subsequent to placing the patient in the Trendelenberg position. Dopamine and isoproterenol have been used most frequently to increase the blood pressure. Pharmacologically, a beta agonist vasopressor should be considered to best counteract CCB toxicity. The administration of calcium salts may be tried to increase the blood pressure and

and ataxia. Transient heart rate changes also occur at these doses; bradycardia is more common then tachycardia. Patients ingesting these amounts of verapamil may be observed at home. Gastrointestinal decontamination is not necessary. If these minor symptoms develop, they will occur within one to two hours and should abate within six to eight hours of exposure. The effects are transient and medical intervention should not be required.

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Major toxicity may occur with doses of verapamil >800 mg. in adults and >240 mg. in children. In addition to the effects described at lower doses, metabolic abnormalities such as hyperglycemia, acidosis, and hyperkalemia have occurred. Elevated blood glucose concentrations may occur due to an inhibition of insulin release [15] while acidosis and hyperglycemia cannot be directly linked to verapamil. Severe central nervous system and cardiovascular effects may develop when these doses are exceeded. Patients have been described as agitated, obtunded and unresponsive. Two patients became cyanotic and required intubation and electromechanical ventilation. Seizures occurred in an adult who overdosed on 2,000 mg. and one child who ingested 400 mg. of verapamil. [16] The authors claim a therapeutic benefit from administration of calcium salts in treating the seizures which developed in this 11 month old child. They gave 2 ml. of 10% calcium chloride which produced "prompt cessation of seizure activity" which had been refractory to two previous doses of 50 mg. of phenobarbital given intramuscularly. The cardiovascular system remained refractory to this treatment and ten minutes after administration of the calcium the child's blood pressure decreased to 38 mm Hg systolic, peripheral pulses became nonpalpable and peripheral perfusion was diminished. Dopamine and isoproterenol were infused simultaneously with normalization of blood pressure and peripheral perfusion. Arrhythmias may also occur when these doses of verapamil are exceeded; supraventricular arrhythmias are common although ventricular abnormalities have also been reported. Bradyarrhythmias may develop and appear difficult to manage.

Death occurred with an estimated ingestion of 1,600 mg. in a fifteen month old child and 1,920 mg. in an adult, but survival has occurred in 13 adult patients ingesting larger amounts who received early gastrointestinal decontamination and supportive treatment in the hospital setting; one patient had ingested 6,400 mg. ofverapamil. A patient ingesting these large amounts of verapamil should be transported by ambulance to a health care facility and promptly receive full gastrointestinal decontamination as previously described. Insulin may be necessary to treat hyperglycemia and sodium bicarbonate may be needed if the patient becomes acidotic. Anticonvulsants may be required to treat seizures. Intravenous diazepam is considered the anticonvulsant of choice for treatment of drug induced seizures, however, the possible benefit of calcium salts in treating seizures has been described. The blood pressure should be continuously monitored and more invasive procedures such as placement of an arterial line may be necessary. Previously recommended treatments for hypotension should be employed. The patient should also receive constant cardiac monitoring. Pacemaking devices may be required to treat bradycardia; atropine does not appear to effectively increase the heart rate in these patients. Additional life-sustaining therapy may be required. Intubation, electromechanical ventilation and CPR have been utilized. The patient should be admitted to an intensive care unit for continued symptomatic and supportive care. Recovery time has ranged from six hours to three days; most patients appeared to improve after 12 hours of intensive care management and monitoring.

SUMMARY

This author has reviewed, summarized and described the characteristics, symptoms, treatment and outcome of acute ingestions of the CCB agents verapamil, nifedipine and diltiazem from cases reported to the AAPCC during 1984. This description was achieved through a retrospective review of the medical record portion of 50 AAPCC Cooperative Poison Center Report Forms submitted by poison centers collecting date for the calendar year 1984. This is the first comprehensive description of poisoning cases involving CCB agents and the first use of the AAPCC National Data Base for this purpose.

On average, patients ingesting diltiazem and nifedipine ingested amounts within the recommended daily therapeutic range, unlike those who ingested verapamil and took greater than five times the upper limit of acceptable daily therapeutic doses. Therefore, the cases exhibiting serious toxicity are composed of verapamil overdoses. Patients ingesting nifedipine developed central nervous system effects at a greater rate than those exposed to verapamil and diltiazem, which is consistent with the side effect profile of nifedipine at therapeutic doses.

Further research must be performed before calcium can be considered as an antidote for an acute overdose of a CCB agent. Although the literature reports claim a therapeutic benefit in treating hypotension and even seizures, these findings could not be confirmed in the study cases.

Ten suicidal literature cases involving verapamil were reviewed and compared to 15 suicidal verapamil exposures in the AAPCC series. This extensive review has culminated in the description of toxic ranges and provision of treatment recommendations as guidelines for the health care professional treating a patient who has ingested a large amount of verapamil.

ILLUSTRATIONS

	481	TOTAL CCB EXPOSURES IN NATIONAL DATABASE
-	242	NO EFFECT (ASYMPTOMATIC)
-	39	CASES FROM CENTERS NOT PARTICIPATING
-	11	CASES NOT RETRIEVABLE BY POISON CENTERS
-	10	CASES UNAVAILABLE DUE TO CLERICAL ERRORS
-	71	UNKNOWN OUTCOMES
-	43	POLYDRUG EXPOSURES
-	7	INGESTION OF OTHER THAN CCB
-	5	NON-AAPCC FORM
-	1	DRUG INFORMATION REQUEST
-	1	DUPLICATE CASE
-	1	ANIMAL EXPOSURE
	50	STUDY CASES DESCRIBED

FIGURE 1 FLOW CHART FOR EXCLUSION OF CASES FROM STUDY

TABLE I

AGE AND SEX DISTRIBUTION AND EXPOSURE INTENT BY PRODUCT

	PRODUCT	ACCIDENTAL Males	ACCIDENTAL Females	ADVERSE REACTION Males	ADVERSE REACTION Females	INTENTIONAL OVERDOSE Males	INTENTIONAL OVERDOSE Females
CHILDREN <5 yrs.	DILTIAZEM	1	1	-	-	-	-
	NIFEDIPINE	1	4	-	-	-	-
	VERAPAMIL[1]	6	3	-	-	-	-
ADULTS >15 yrs.	DILTIAZEM	1	2	-	1	1	-
	NIFEDIPINE	1	2	1	2	-	2
	VERAPAMIL	1	3	1	-	4	11

[1] The sex of one child ingesting verapamil was not recorded.

TABLE II

TIME BETWEEN INGESTION AND POISON CENTER CONTACT FOR PATIENTS WITH KNOWN INGESTION TIMES (N=38)[1]

TIME DELAY	ADULTS # (%)	CHILDREN # (%)	TOTAL # (%)	CUM. TOTAL # (%)
<5 MIN.	4 (16.7)	4 (28.6)	8 (21.0)	8 (21.0)
5 MIN.	1 (4.2)	4 (28.6)	5 (13.1)	13 (34.2)
10 MIN.	1 (4.2)	2 (14.3)	3 (7.9)	16 (42.1)
30 MIN.	3 (12.5)	3 (21.4)	6 (15.8)	22 (57.9)
60 MIN.	5 (20.8)	0	5 (13.1)	27 (71.0)
120 MIN.	3 (12.5)	1 (7.1)	4 (10.5)	31 (81.5)
180 MIN.	2 (8.3)	0	2 (5.3)	33 (86.8)
240 MIN.	2 (8.3)	0	2 (5.3)	35 (92.1)
360 MIN.	2 (8.3)	0	2 (5.3)	37 (97.4)
>360 MIN.	1 (4.2)	0	1 (2.6)	38 (100.0)

[1] Excluded from this table are four patients who ingested the CCB over a chronic period of time and eight patients for whom the time between ingestion and poison center contact was unknown.

TABLE III

DOSE INGESTED BY PRODUCT AND AGE CATEGORY

	PRODUCT	MEAN	RANGE	THERAPEUTIC RANGE
CHILDREN <5 yrs.	DILTIAZEM (N=2)	38 MG	15-60 MG	NOT AVAILABLE
	NIFEDIPINE (N=3)	10 MG	10 MG	
	VERAPAMIL (N=6)	710 MG	40-1,600 MG	
ADULTS >15 yrs.	DILTIAZEM (N=3)	60 MG	60 MG	180-240 MG/DAY
	NIFEDIPINE (N=7)	87 MG	10-300 MG	120-180 MG/DAY
	VERAPAMIL (N=16)	2,871 MG	180-21,600 MG	320-480 MG/DAY

TABLE IV

TOXIC EFFECTS BY ORGAN SYSTEM IN STUDY CASES [1]

ORGAN SYSTEM	ADULTS (N=33) #	CHILDREN (N=13)[2] #	TOTAL (N=50) #	(%)
CARDIOVASCULAR				
HR Change[3]	11	0	11	(22.0)
Hypotension	17	2	19	(38.0)
Arrhythmias	10	3	13	(26.0)
CNS[4]	21	3	24	(48.0)
DERMAL[5]	2	2	4	(8.0)
GI[6]	7	4	11	(22.0)
OTHER[7]	3	1	4	(8.0)

1 Total percentage exceeds 100% because some patients had more than one organ system affected.

2 The remaining four children vomited after receiving ipecac syrup.

3 All patients ingested verapamil.

4 Includes lightheadedness, dizziness, headache, shakiness, lethargy, sleepiness or drowsiness, ataxia, agitation and combativeness.

5 Includes red lips, red cheeks, flushing, petecchiae, and a macular rash with pruritis.

6 Includes nausea and vomiting and one case of acute gastrointestinal hemorrhage reported on autopsy; all symptoms occurred prior to adminstration of gastrointestinal decontamination measures.

7 Includes one adult with hyperglycemia and another adult with cyanosis, a third adult with digital ischemia, a child with hyperkalemia, acute renal failure and adult respiratory distress syndrome; due to the complexity of the case, these effects cannot be definitively attributed to the CCB.

TABLE V

TREATMENT SITE AND DISPOSITION OF STUDY SUBJECTS

	REASON	HCF[1] ADMITTED	TREATED & RELEASED	DIED	non-HCF[2]
CHILDREN	ACCIDENTAL	5	5	1	6
ADULTS	ACCIDENTAL/ ADVERSE REACTION	1	6	-	8
	INTENTIONAL OVERDOSE	15[3]	1	2	-
	TOTAL	21	12	3	14

[1] Includes all patients evaluated at a health care facility.
[2] Includes subjects observed at home and those instructed to inform their private physician.
[3] One subject was admitted for psychiatric evaluation.

TABLE VI

GASTROINTESTINAL DECONTAMINATION METHODS USED IN STUDY CASES [1]

TREATMENT	ADULTS #	CHILDREN #	TOTAL #	(%)
IPECAC SYRUP	5	11	16	(32.0)
LAVAGE	4	1	5	(10.0)
ACTIVATED CHARCOAL	9	2	11	(22.0)
CATHARTIC	4	3	7	(14.0)
FULL DECONTAMINATION[2]	2	2	4	(8.0)

1 Percentage does not total 100% because some patients received more than one treatment and others did not receive treatment; 22 patients received some form of gastrointestinal decontamination.

2 Includes ipecac or lavage, activated charcoal and a cathartic.

TABLE VII

SPECIFIC TREATMENTS USED IN STUDY CASES[1]

TREATMENT	ADULTS (N=33) #	CHILDREN (N=17) #	TOTAL (N=50) # (%)
CALCIUM SALTS[2]	6	1	7 (14.0)
FLUID CHALLENGE	7	0	7 (14.0)
VASOPRESSORS[2]	9	0	9 (18.0)
CARDIAC PACING[2]	2	0	2 (4.0)
CARDIOPULM. RESUSC.[2]	2	1	3 (6.0)
DEFIBRILLATION[2]	1	0	1 (3.0)
OTHER[3]	6	0	6 (12.0)

1 Percentage does not total 100% because some patients received more than one treatment and others did not require treatment; 21 patients received these treatments.

2 All patients ingested verapamil.

3 Includes extracorporeal removal, lidocaine, insulin, oral fluids, antihistamines and a topical steroid cream.

APPENDIX A

AAPCC COOPERATIVE POISON CENTER REPORT FORM

APPENDIX B

SAMPLE LETTER SENT TO POISON CENTERS

50 North Medical Drive, Building
Salt Lake City, Utah 84132

Poison Information and Emergenc
(801) 581-2151
Utah Toll-Free
(800) 662-0062
Administration
(801) 581-7504

The Intermountain Regional
POISON CONTROL CENTER

J. C. Veltri, Pharm.D.
Intermountain Reg. PCC
50 North Medical Drive
Salt Lake City, UT 84132

Dear Doctor Veltri:

You recently agreed to release your center code for an investigation of calcium channel blocker exposures during 1984. As the principle investigator of this study, I am requesting your cooperation in obtaining more detailed information about the cases. My research project is a requirement for the Doctor of Pharmacy degree at the University of Utah and the objective of my study is to describe the demographic characteristics, frequency, and severity of acute ingestions involving calcium channel blocking agents (verapamil, diltiazem, nifedipine). I expect to achieve this goal through a retrospective review of the original medical record portion of the AAPCC Data Collection Form.

The following symptomatic cases were reported by your center:

Form#	Date	Hour	Drug

It would be most helpful if you could locate the medical record portion of the forms, photocopy them, and send the copies to me in the enclosed envelope.

Investigational Review Board approval has been obtained from the University of Utah. Patient confidentiality is assured. Please be informed that strict confidence will be maintained and no attempt will be made to contact the subject. You may, however, blacken names and phone numbers before forwarding the photocopies. I am requesting photocopies of the forms to allow retrieval of data which are not captured on the data collection portion (dose, symptoms manifested, etc.).

I sincerely hope you can find time to assist me in this research endeavor. If questions arise or you are unable to comply with my request, please contact me at the Intermountain Regional Poison Control Center so that alternative means of accessing the data can be arranged: 1-800-662-0062.

Respectfully,

Mary A. McCormick
Poison Information Pharmacist
Intermountain Regional Poison Control Center

APPENDIX C

CASE REPORTS OF DEATHS DUE TO VERAPAMIL

Three of the four deaths reported in the AAPCC database in 1984 were included in the study cases; one of the fatal cases was excluded from this report because the patient's chart indicated she had concurrently ingested metoprolol and cimetidine. The history, symptoms and treatment course of these patients follow.

Case #1: A 37 year old female arrived at an emergency room at 14:12 and was described as combative and moaning occasionally with fixed and dilated pupils. The patient had been put to bed by family members after falling from a ladder onto a broken table and when checked on later was found in this condition. A prescription for verapamil filled the day before was found nearby and the amount ingested was estimated at 1,920 mg., although the time of ingestion was unknown. After arrival, the patient was cyanotic, hypotensive, and bradycardic with a pulse of 32; orbital and nasal fractures were noted as were hematomas of the left breast and cheek. The patient was endotracheally intubated and mechanically ventilated, intravenous isoproterenol was initiated, and a central venous pressure line and pacemaker were inserted shortly after arrival at the emergency department. The patient was cardioverted twice for ventricular fibrillation. Norepinephrine was added to the isoproterenol as a pressor agent, however, the patient continued to deteriorate and cardiopulmonary resuscitation (CPR) was initiated. CPR was stopped approximately 30 minutes after initiation and the patient was pronounced dead.

Case #2: The poison center was called by a physician regarding a 15 month old male who had possibly ingested 1,600 mg. of verapamil five hours prior the to call. The child was described as "unstable" in the intensive care unit. Nine hours after ingestion the child's condition apparently deteriorated and he experienced a cardiac arrest and was noted to have a serum potassium of 10 mEq/l. A follow-up call placed by the poison center 12 hours after exposure determined that the child had died. Pathological findings according to the medical examiner's report were multiple cardiac arrhythmias and clinical hypotension, adult respiratory distress syndrome, hypoxic encephalopathy, acute renal failure and diffuse gastrointestinal hemorrhage.

Case #3: The dispatcher for paramedics at the scene contacted the poison center about a 35 year old male who had allegedly ingested 21,600 mg. of verapamil one-half hour prior to the call. At 11:30 the receiving emergency room described the patient as "initially stable in the field", but a widened QRS interval was noted on arrival in the emergency room. Calcium chloride (dose unknown) was given and apparently corrected the electrocardiographic abnormality. The systolic blood pressure was 50-60 mm Hg, dopamine and isoproterenol were administered and a cardiac pacemaker was placed in the patient. At 14:10 the emergency room reported that the patient had expired after experiencing third degree heart block and a junctional rhythm prior to asystole. Resuscitation efforts failed.

REFERENCES

1. Porter CJ, Garson A, Gillette PC. Verapamil: an effective calcium blocking agent for pediatric patients. Pediatrics 1983;71:748-755.

2. Cho C, Pruitt AW. Therapeutic uses of calcium channel-blocking drugs in the young. Am J Dis Chil 1986; 140:360-366.

3. Skoutakis VA, Carter CA, Wojciechowski NJ, et al. Management of intoxications with calcium channel blockers. Clin Tox Cons 1984;6:51-67.

4. DeFaire U, Lundman T. Attempted suicide with verapamil. Eur J Cardiol 1977;6:195-198.

5. Gelbke HP, Schlicht HJ, Schmidt GG. Fatal poisoning with verapamil. Arch Toxicol 1977;37:89-94.

6. Perkins CM. Serious verapamil poisoning, treatment with calcium gluconate. Br Med J 1978;21:1127.

7. Candell J, Valle V, Soler M, et al. Acute intoxication with verapamil. Chest 1979;75:200-201.

8. DaSilva DA, Demelo RA, Filho JPJ. Verapamil acute self poisoning. Clin Toxicol 1979;14:361-367.

9. Moroni F, Mannaioni PF. Calcium gluconate and hypertonic sodium chloride in a case of massive verapamil poisoning. Clin Toxicol 1980;17:395-400.

10. Immonen P, Linkola A, Waris E. Three cases of verapamil poisoning. Int J Cardiol 1981;1:101-105.

11. Woie L, Storstein L. Successful treatment of suicidal verapamil poisoning with calcium gluconate. Eur Heart J 1981;2:239-242.

12. Lipman J, Jardine A, Roos C, et al. Intravenous calcium chloride as an antidote to verapamil-induced hypotension. Intensive Care Med 1982; 8:55-57.

13. Crump BJ, Holt DW, Vale JA. Lack of response to intravenous calcium in severe verapamil poisoning. Lancet 1982;1:939-940.

14. Orr GM, Bodansky HJ, Dymond DS, et al. Fatal verapamil overdose. Lancet 1982;2:1218.

15. Enyeart J, Bodansky HJ, Dymond DS, et al. Profound hyperglycemia and metabolic acidosis after verapamil overdose. J Am Coll Cardiol 1983;2:1228-1231.

16. Passal DB, Crespin FH. Verapamil poisoning in an infant. Pediatrics 1984; 73:543-545.

17. Shiffe H, Ziupa J, Schollmeyer P. Clinical features and management of nifedipine overdosage in a patient with renal insufficiency. J Tox Clin Tox 1984;22:387.

18. Henry M, Kay MM, Vicellio P. Cardiogenic shock associated with calcium-channel and beta-blockers. Am J Emerg Med 1985; 3:334-336.

19. Hattori VT, Mandel WJ, Peter T. Calcium for myocardial depression from verapamil. N Eng J Med 1982; 306:238.

20. Snover SW, Bocchino V. Massive diltiazem overdose. Ann Emerg Med 1986; 15: 129-132.

21. Litovitz T, Veltri J. 1984 annual report of the American Association of Poison Control Centers national data collection system. Amer J Emerg Med 1985; 3:423-450.

22. Weissman MM. The epidemiology of suicide attempts, 1960-1971. Arch Gen Psychiatry 1974; 30:737-746.

23. Fazen LE, Lovejoy FH, Crone RK. Acute poisoning in a children's hospital: A 2-year experience. Pediatrics 1986; 77:144-151.

24. Talbert RL, Bussey HI. Update on calcium channel blocking agents. Clinical Pharmacy 1983; 2:403-416.

25. Rumack BH, Temple A. Lomotil poisoning. Pediatrics 1974;53:495-500.

26. Stein B, Volans GW. Dixarit overdose: the problem of attractive tablets. Br Med J 1978;2:667-668.

27. Wagner JG, Rocchini AP, Vasiliades J. Prediction of steady state verapamil concentration in children and adults. Clin Pharmacol Ther 1982;32:172-181.

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PROFESSIONAL AFFILIATIONS

1986 - Present	Member, California Society of Hospital Pharmacists
1984 - 1986	Member, Utah Society of Hospital Pharmacists
1984 - 1986	Planning Committee Member, Camp Superkids, American Lung Association of Utah
1983 - 1984	Board Member, New England Region of the National Reye Syndrome Foundation
1981 - Present	Member, American Society of Hospital Pharmacists
1981 - 1985	Member, Massachusetts Society of Hospital Pharmacists
1980 - Present	Member, American Association of Poison Control Centers
1980 - 1984	Fraternity Advisor, Lambda Kappa Sigma, Professional Fraternity for Women in Pharmacy
1975 - Present	Member, Lambda Kappa Sigma, Professional Fraternity for Women in Pharmacy

PROFESSIONAL LICENSURE

1986	Registered Pharmacist - State of California
1984	Pharmacist Intern - State of Utah
1983	Certified Poison Information Specialist, American Association of Poison Control Centers
1980	Registered Pharmacist - Commonwealth of Massachusetts

PUBLICATIONS

Gaudreault P, McCormick MA, Lacouture PG, Lovejoy FH Jr. Poisoning exposures and use of ipecac in children less than 1 year old. Ann Emerg Med 1986; 15:808-810.

McCormick MA, Lacouture PG, Gaudreault P, Lovejoy FH Jr. Hazards associated with diaper changing. JAMA 1982; 248:2159-2160.

McCormick MA, Easom JM. Insect stings: the pharmacist's role in counseling patients in the care and prevention of painful stings. Natl Assoc Retail Druggists J 1981; 103: 51-55.